REMARKS

Claims 29, 32, and 43 are amended herein. Claims 29-33 and 43-49 are pending in the application. Claims 1-28 and 34-42 are previously cancelled. Thus, claims 29-33 and 43-49 are under examination. Support for the amendments to claims 29, 32 and 43 can be found throughout the specification, for example at paragraphs [0026] and [0027] of the published application.

Applicants thank the Examiner for withdrawing the rejection of claims 29, 32, and 43 under 35 U.S.C. §102(e) as allegedly being anticipated by Haffner et al. (US 2004/0167341).

Examiner Interview

Applicants express appreciation to Examiner Lum and Examiner Jung for conducting an in person interview with Applicants on November 19, 2009. During the interview, Applicants discussed the pending claims and the art references cited by the Examiner in the Office Action mailed on August 7, 2009, details of which are described in the following sections. Applicants further express appreciation for the Examiner's willingness to consider this supplemental amendment.

Claim Rejections – 35 U.S.C. § 103

A. Claims 29, 32, 43, and 47-49.

Claims 29, 32, 43 and 47-49 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cheng et al. (J. Am. Coll. Cardiol., vol. 37, pp 386-391 (2001)) ("Cheng") in view of Haffner et al. (U.S. Patent App. No. 2004/0167341) ("Haffner"). Applicants respectfully traverse this rejection.

The Examiner asserts that Cheng describes a "BNP guided treatment regimen" which "uses BNP measurements as an indicator to adjust medication for patients" and "provides effective care while reducing invasive hemodynamic monitoring." Thus, the Examiner asserts that Cheng teaches the "selecting," "performing" and "determining" steps as recited in claims

29, 32, and 43. The Examiner acknowledges that Cheng does not teach the "administering" step of these claims, but asserts that the administration of a DPP-IV inhibitor for treatment of congestive heart failure is taught by Haffner. The Examiner concludes that "one of ordinary skill in the art would have found it obvious to modify Cheng's method by adding Haffner's technique of treating congestive heart disease with a DPP-IV inhibitor." (Office Action at pg 3)

In order to establish a *prima facie* case of obviousness, the Examiner must demonstrate that the prior art (i) teaches or suggests every claim limitation, (ii) provides a motivation to combine (or modify) the teachings of the selected references, and (iii) provides a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP §2143. Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness. *KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1741 (2007) (quoting *In re Kahn*, 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)). The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, not in applicant's disclosure. *In re Vaeck*, 947 F.2d 488. Thus, in order to establish a prima facie case of obviousness, it is necessary for the Examiner to demonstrate that the references teach or suggest each element of the claims and that there is a reasoned basis to combine the teachings of the cited references and a reasonable expectation of success.

Claims 29, 32 and 43 are amended herein to recite "performing an assay to specifically detect a B-type natriuretic peptide in a sample obtained from said subject, wherein said natriuretic peptide is BNP_{77-108} or BNP_{1-108}". Neither the primary reference, Cheng, nor the secondary reference, Haffner, teach an assay which specifically detects BNP_{77-108} or BNP_{1-108}. As the references, either alone or in combination, fail to teach each element of the pending claims, they cannot render claims 29, 32 and 43 (or any claims depending therefrom) obvious.

Contrary to the Examiner's assertion, one of skill in the art would not be motivated to combine the teachings of Cheng and Haffner. Indeed, a fair reading of the entire Cheng reference would lead one of skill in the art to the opposite conclusion, e.g., that a DPP-IV

inhibitor should not be used to treat congestive heart failure. For example, Figures 1 and 2 of Cheng, show that a decrease in the level of BNP correlates to better clinical outcome. Cheng summarizes these results, stating "[p]atients who had good outcomes tended to be characterized by decreases in . . . BNP levels during hospitalization" and "subjects who died in the hospital had rising BNP levels." Cheng, pg. 387, right column, last full paragraph (emphasis added). Additionally, Cheng states that the data "shows a significant association between [readmission and/or death] and rising versus falling BNP levels" but that "[p]atients with falling BNP levels during treatment had only a 16% [readmission and/or death] rate." *Id.*, paragraph spanning pg. 367-368 (emphasis added). Thus, Cheng clearly teaches that falling or lower BNP levels are associated with a positive clinical outcome.

Haffner teaches utilizing an inhibitor of a post proline/analine cleaving protease (e.g., DPP-IV inhibitor) to treat a laundry list of unrelated diseases, including congestive heart failure. However, Haffner provides no treatment guidelines or data showing that such treatment is effective. Additionally, Haffner does not disclose that the inhibitors disclosed function on BNP and, therefore, provides no suggestion or correlation to the BNP of Cheng. Thus, there is no suggestion for combining Haffner with Cheng for the BNP guided therapy for treatment of decompensated heart failure. It is improper to use Applicants' disclosure in formulating a rejection.

As disclosed in the present application (but not the combined references), DPP inhibitors prevent degradation of BNP and can be administered "for treating a subject in need of increased natriuretic peptide function." (paragraph [0052], see also paragraph [0046]) (emphasis added). Thus, it would not be obvious to one of skill in the art to combine the DPP-IV inhibitor of Haffner – which would increase or stabilize the level of BNP in a subject – with the method of Cheng. Indeed, because Cheng demonstrates and concludes that lowered or falling BNP levels correlate with improved clinical outcome, Cheng teaches away from treating a patient so as to increase or stabilize BNP levels. Because Cheng teaches away from the use of a DPP-IV inhibitor, one of skill in the art would not be motivated to combine the references and would

have no reasonable expectation of success. Thus, the Examiner has failed to establish a *prima facie* case of obviousness.

With regard to claims 47-49 (which depend from claims 23, 32, and 43, respectively), the Examiner asserts that Cheng describes a fluorescence immunoassay to test for BNP. Such teaching does not cure the defects in the combination of Cheng and Haffner as described and, thus, the Examiner has not established a *prima facie* case of obviousness for claims 47-49.

For at least the foregoing reasons, the cited references, either alone, or in combination, cannot render obvious Applicants' claims 29, 32, 43 and 47-49. Claims 29, 32, 43 and 47-49 are therefore allowable under 35 U.S.C. § 103(a) and the rejection should be withdrawn.

B. Claims 30 and 44

Claims 30 and 44 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cheng in view of Haffner and further in view of De Meester et al., (Biochem. Pharmacol., vol. 54, pp. 173-179 (1997)) ("De Meester"). Applicants respectfully traverse this rejection.

Claims 30 and 44 depend from claims 29 and 43 respectively. As such, claims 30 and 44 incorporate all limitations of claims 29 and 43 respectively. As discussed above, the Cheng and Haffner references do not teach each element of claims 29 and 43. De Meester is cited solely for the disclosure of a DPP inhibitor comprising a phosphonate moiety (propidine). De Meester does not disclose "performing an assay to specifically detect a B-type natriuretic peptide in a sample obtained from said subject, wherein said natriuretic peptide is BNP_{77-108} or BNP_{1-108}" as recited. Thus, the cited references, alone or in combination do not teach or suggest each element of claims 30 and 44.

Additionally, the combination of Cheng and Haffner is improper and does not establish a *prima facie* case of obviousness for claims 29 and 43. De Meester does not disclose the treatment of any disease with propidine, but merely demonstrates *in vivo* activity of propidine. Such disclosure does not provide one of skill in the art with motivation to combine Cheng and Haffner or provide a reasonable expectation of success. As such, De Meester does not cure the

deficiencies in the Cheng and Haffner references. Thus, the Examiner has not established a *prima facie* case of obviousness for claims 30 and 44.

For at least the foregoing reasons, the cited references, either alone, or in combination, cannot render obvious Applicants' claims 30 and 44. Claims 30 and 44 are therefore allowable under 35 U.S.C. § 103(a) and the rejection should be withdrawn.

C. Claims 31 and 45.

Claims 31 and 45 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cheng in view of Haffner and further in view of Bergmann et al., (US 6,756,483) ("Bergmann"). Applicants respectfully traverse this rejection.

Claims 31 and 45 depend from claims 29 and 43 respectively. As such, claims 31 and 45 incorporate all limitations of claims 29 and 43 respectively. As discussed above, the Cheng and Haffner references do not teach each element of claims 29 and 43. Bergmann is cited solely for the disclosure of a DPP inhibitor comprising an antibody or antibody fragment. Bergmann does not disclose "performing an assay to specifically detect a B-type natriuretic peptide in a sample obtained from said subject, wherein said natriuretic peptide is BNP_{77-108} or BNP_{1-108}" as recited. As such, Bergmann does not cure the deficiencies in the Cheng and Haffner references. Thus, the cited references, alone or in combination do not teach or suggest each element of claims 31 and 45.

Additionally, as discussed above, the combination of Haffner and Cheng is improper and does not establish a *prima facie* case of obviousness for claims 29 and 43. Bergmann, however, does not disclose the use of a DPP inhibitor to treat any disease. Such disclosure does not provide one of skill in the art with motivation to combine Cheng and Haffner or provide a reasonable expectation of success. As such, Bergmann does not cure the deficiencies in the Cheng and Haffner references. Thus, the Examiner has not established a *prima facie* case of obviousness for claims 31 and 45.

For at least the foregoing reasons, the cited references, either alone, or in combination, cannot render obvious Applicants' claims 31 and 45. Claims 31 and 45 are therefore allowable under 35 U.S.C. § 103(a) and the rejection should be withdrawn.

D. Claims 33 and 46.

Claims 33 and 46 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Cheng in view of Haffner and further in view of Mills et al. (Journal of the American College of Cardiology, vol. 34, no. 1, pp.155-162 (1999)) ("Mills"). Applicants respectfully traverse this rejection.

Claims 33 and 46 depend from claims 32 and 43 respectively. As such, claims 33 and 46 incorporate all limitations of claims 32 and 43 respectively. As discussed above, the Cheng and Haffner references do not teach each element of claims 29 and 43. Mills is cited solely for the disclosure that human recombinant B-type natriuretic peptide is used therapeutically in decompensated heart failure. Mills does not disclose "performing an assay to specifically detect a B-type natriuretic peptide in a sample obtained from said subject, wherein said natriuretic peptide is BNP_{77-108} or BNP_{1-108}" as recited. As such, Mills does not cure the deficiencies in the Cheng and Haffner references. Thus, the cited references, alone or in combination do not teach or suggest each element of claims 33 and 46.

Additionally, as discussed above, the combination of Haffner and Cheng is improper and does not establish a *prima facie* case of obviousness for claims 32 and 43. The primary reference, Cheng, demonstrates and concludes that lowered or falling BNP levels correlate with improved clinical outcome, thus teaching away from treating a patient so as to increase or stabilize BNP levels. Thus, it would not be obvious to one of skill in the art to combine the DPP-IV inhibitor of Haffner or the recombinant B-type natriuretic peptide (nesitiride) of Mills – both of which would increase or stabilize the level of BNP in a subject –with the method of Cheng. The disclosure of Mills does not provide one of skill in the art with motivation to combine Cheng and Haffner or provide a reasonable expectation of success. Additionally, Cheng teaches away from combination with Haffner and Mills, alone or in combination. As such, Mills does

not cure the deficiencies in the Cheng and Haffner references. Thus, the Examiner has not established a *prima facie* case of obviousness for claims 33 and 46.

For at least the foregoing reasons, the cited references, either alone, or in combination, cannot render obvious Applicants' claims 33 and 46. Claims 33 and 46 are therefore allowable under 35 U.S.C. § 103(a) and the rejection should be withdrawn.

CONCLUSION

Applicant respectfully submits that all rejections and objections have been obviated and that the pending claims are in condition for allowance. An early notice to that effect is earnestly solicited. Should any matters remain outstanding, the Examiner is encouraged to contact the undersigned at the telephone number listed below so that they may be resolved without the need for an additional action.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16 1.17, or credit any overpayment, to Deposit Account No. 23-2415. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extensions under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 23-2415.

Respectfully submitted,

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